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Alteration of mitochondrial dynamics and calcium buffering in cerebellar degeneration

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Degeneration of Purkinje cells is the most common neuropathological feature of cerebellar ataxias. Purkinje cells are characterized by a large soma and extensive dendritic trees exposed to high cytosolic calcium concentrations. Synapses of Purkinje cell dendrites need a more precise control of calcium homeostasis compared to other neurons, implying higher levels of ATP and higher calcium buffering power. These features suggest that proper mitochondrial functionality and distribution to microdomains of large ion fluxes represent crucial issues in Purkinje cells. Indeed, mitochondria not only provide ATP to active calcium clearance systems at the plasma membrane, but also exert themselves a fine shaping of calcium signals by accumulating calcium into the matrix.
Experimental mouse models in which key regulators of mitochondrial fusion or fission (MFN2 or DRP1) are specifically ablated in Purkinje cells develop defects in motor coordination and Purkinje cell degeneration associated to aberrant mitochondrial ultrastructure and altered mitochondrial distribution.
We will discuss the critical dependence of Purkinje cells on mitochondrial dynamics in physiopathological conditions, i.e. in two inherited forms of cerebellar ataxia: SCA28 and ARSACS. Even if the triggering events are opposite (i.e. mitochondrial fragmentation in SCA28 and mitochondrial hyperfusion in ARSACS) we found that they both result in altered mitochondrial distribution in the dendrites of Purkinje cells and finally in neurodegeneration.
The findings highlight defective mitochondrial dynamics as a common pathogenetic pathway to PC degeneration in cerebellar ataxias, that can be targeted for therapy.